

Independent evidence-based health care

This month *Bandolier* returns to the difficult world of readers' questions. There is a big overlap with another world, that of little evidence. So answering readers' questions often means delving into areas where we have to make the best of what we have.

One of these simple questions to which the only answer is long, complicated, and unsatisfactory is that of whether stopping statins is dangerous. Many (most?) people who start statins do eventually stop them, but why on earth should there be any danger? Actually, there is some interesting biology behind possible problems, and at least two bits of evidence hinting that theory and practice are not strangers.

The whole business of pneumococcal vaccination is also a perennial. Most of any possible benefit seems to be in incredibly rare outcomes, where randomised trials or even meta-analysis of randomised trials collect too few events to be sure of the result. Good observational studies coming up with the same answer give us much more confidence.

Subscription renewal

For many *Bandolier* readers, this July issue will mark the last paper copy they will have under their present subscription arrangement. You should have had a renewal letter, but if you have mislaid it, or forgotten to renew, don't panic.

On page 8 of this issue is a panel giving you several options about how to renew your subscription. There is also a reminder that large discounts are available for bulk purchase, for instance for a PCO, with local distribution.

And the price is the same now as it has been for most of *Bandolier's* 10 years, despite hikes in paper, postage and printing.

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STATINS AND THE LAW OF UNINTENDED CONSEQUENCES

A reader asked *Bandolier* whether it was true that it was dangerous to stop taking statins. Given that statins are among the safest of drugs, this seemed a rather curious question to which the answer was blisteringly obvious. If statins were given to prevent something bad happening, then stopping them might make the bad thing more likely to happen. A quick search turned up two pieces of evidence imply that stopping or changing statins could increase vascular risk by about three times. There are some complexities in the biology that might make this an interesting area to keep an eye on.

Changing statins in primary care [1]

This report was an audit of all patients who had changed their statin in the Otago region of New Zealand in a response to a reference pricing scheme. There were 126 such patients, and their hospital records were examined for fasting lipids and hospital admission for unstable angina, myocardial infarction, thrombotic stroke or peripheral artery occlusion for the six months before and after substitution of fluvastatin for simvastatin.

The mean dose of simvastatin of 22 mg was changed to a mean dose of 37 mg of fluvastatin. The change was accompanied by a significant rise in total cholesterol of 18%, LDL cholesterol by 34% and triglyceride by 13%. Significant increases occurred in 94% of the patients.

There was also a three-fold increase in thrombotic events (Table 1), from nine in the last six months on simvastatin to 27 in the first six months on fluvastatin.

Table 1: Thrombotic events in six months before and after change of statin

	Simvastatin	Fluvastatin
Mean dose (mg)	22	37
Events over six months		
Myocardial infarction	2	6
Unstable angina	7	15
Non-haemorrhagic stroke	0	4
Acute limb ischaemia	0	2
Total vascular events	9	27

126 patients over six months before and after substitution of fluvastatin for simvastatin

Withdrawing statins in patients with acute coronary disease [2]

A randomised trial set out to test the efficacy of platelet receptor inhibition in the first 40 hours after the onset of chest pain in 3232 patients. Those results are of no interest here, but a retrospective analysis examined the outcomes of death, myocardial infarction, ischaemia and revascularisation in the 30 days after onset of chest pain according to statin therapy. Where there were full records:

- ◆ 1151 patients had no statins at any time,
- ◆ 369 had a statin treatment before their chest pain and continued with the statin after the onset of chest pain, and
- ◆ 86 had statin treatment before the onset of chest pain but had the statin discontinued at or after admission with chest pain.

Patients in these three groups were similar (age about 67 years, mostly men). Those on statin treatment had more hypercholesterolaemia diagnoses, but a 10% lower median total cholesterol than those who did not receive statins. Total cholesterol did not change in the 72 hours after withdrawal.

The main difference was in the rates of death and myocardial infarction in the 30 days after onset of chest pain. Patients on statins before and after admission had lower event rates than those not on statins (Figure 1). Those who had statin withdrawn had higher rates, not just higher than those continuing on statins (relative risk 2.9; 1.6 to 6.3), but higher than those never treated with a statin, though not significantly so (1.7; 0.9 to 3.6).

Comment

It may be pure coincidence that in both these reports there was a three-fold increased risk of an event after stopping a

statin or changing to an ineffective dose, but it was the expected result. Neither study is definitive and merely serve to generate hypotheses, though ethics for the trial needed to prove the hypothesis may be difficult to come by, especially if the idea was to prove a larger than expected effect.

Statins are likely to do things other than just affect cholesterol levels. Endothelial nitric oxide production, leukocyte adhesion, platelet activation and LDL oxidation are all postulated mechanisms for which there is some experimental evidence. That is all very academic, but a better handle on the risk with stopping statins would be welcome.

There is an enormous experiment going on, in which millions of people are being prescribed statins and begin to take them. But most patients stop taking their statins after some time. If there is an increased risk with stopping, might an unintended consequence be that we actually cause more thrombotic events?

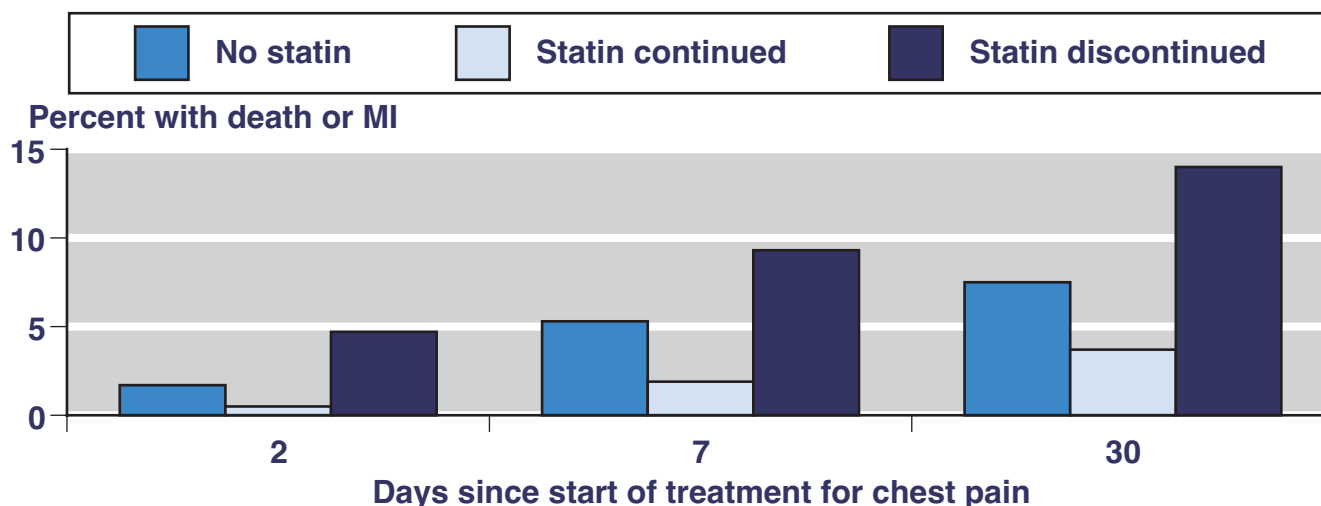
Unintended consequences also come from tinkering with therapy. The Otago “experiment” came from changes in reimbursement policy, so patients received insufficient doses of a less potent drug that probably altered their lipid control for the worse. When statin was changed from simvastatin to atorvastatin and lipid control changed for the *better*, the number of thrombotic events after the change was low, and no different from before the change [3].

Perhaps the take home message is not to mess about with statin therapy without a very good reason, and to make sure that lipid control is not impaired. Sure we need more data, but we know how to avoid the law of unintended consequences.

References:

- 1 M Thomas, J Mann. Increased thrombotic vascular events after change of statin. *Lancet* 1998 352: 1830-1831.
- 2 C Heeschen et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation* 2002 105: 1446-1452.
- 3 AS Wierzbicki et al. Increased thrombotic vascular events after change of statin. *Lancet* 1999 353: 845.

Figure 1: Outcome of death or MI for patients never treated with a statin, those in whom statin continues after onset of chest pain, and those in whom statin was discontinued after onset of chest pain



COPD PREVALENCE

How many people have chronic obstructive pulmonary disease? A deceptively simple question, this, according to a systematic review of prevalence rates [1]. It concludes that we just don't know, but it is probably more than we think.

The problems are the ones that any of us would think of, namely the definition of the population in which we are interested, the definition of what COPD is, and how COPD is measured. What we seem to have is a number of goalposts all moving randomly in different directions .

Systematic review

The review used a single MEDLINE search designed to detect any studies that might have quantified the prevalence of COPD in countries or regions. Studies of interest were those that had a total population estimate or sex or age specific estimate of COPD and had methods sufficiently clear to establish what the sampling strategy was, what the diagnostic criteria were, and how the diagnosis was made.

Results

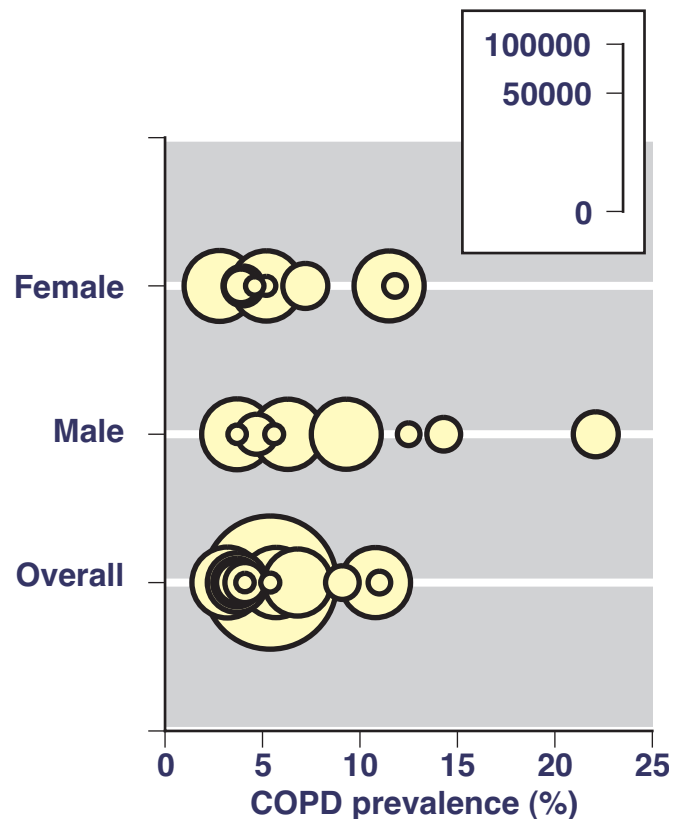
The authors found 32 sources of prevalence data, most in 17 single countries in the developed world. Most of the studies examined adults, but often with age restrictions and both younger and older ages.

Methods used to diagnose COPD included:

- ◆ Spirometry, with or without clinical examination. These were not uniform, and usually involved some relationship of FEV1 to slow or forced vital capacity, with the definition of COPD as being below some percentage of predicted. That percentage was itself variable.
- ◆ Presence of respiratory symptoms. Most of these studies used the MRC criteria of cough on most days of the week for three months of the year for at least two years.
- ◆ Patient reported symptoms. Results here were generally derived from a patient's report of a physician's diagnosis.
- ◆ Expert opinion. This came from a WHO report on global health statistics, where disease experts made estimates based on published or unpublished studies, or informed estimates, followed by review at various stages.

Prevalence estimates varied, but the largest discrepancy was between the WHO expert opinion estimate of a world prevalence of 0.8%, and all other studies where the estimate of overall prevalence was between 1% and 18%, with most between 3% and 10%. There were too many variables to determine what the differences were in different ages, or using different diagnostic methods, but there was a tendency for prevalence to be higher in men.

Figure 1: Estimates of COPD prevalence in adults



Estimates of prevalence where the population was large enough to be representative, in theory, of the entire population of a country, are shown in Figure 1, overall, and for men and women separately. Most estimates again were between 3% and 10%.

Comment

The simple answer to our simple question is that we really don't know the prevalence of COPD with any accuracy, but it is probably more than we thought, and we probably do not pay sufficient attention to it.

Definition makes profound differences. One Italian study applied various criteria used in Europe and the USA to about 2,000 people in a rural area in the Po valley aged 25 or older, and found that COPD prevalence could be as low as 11% or as high as 57%, depending on age and definition.

Definitely some fertile ground for respiratory physicians and physiologists, epidemiologists, primary care professionals, health economists and the like here.

What might this mean for a UK population, where about 40% of the population is aged 45 years or more, the age where COPD is most likely to be found? Applying the range of estimates found for COPD, this would mean between about 1,000 and 4,000 cases per 100,000 population. This not an insignificant burden.

References:

- 1 RJ Halbert et al. Interpreting COPD prevalence estimates. What is the true burden of disease? Chest 2003 123: 1684-1692.

LOW CARBOHYDRATE DIETS – TWO RCTs AND A SYSTEMATIC REVIEW

Low carbohydrate diets seems to have replaced house prices as a topic of dinner table conversation. Arguments rage between weight lost (spectacular numbers of stones, pounds or kilograms) and harm done (cholesterol raised, heart attacks suffered). The trouble is that some iron-willed folk would probably make any diet work through rigid calorie restriction, while others are so unfit that an exciting episode of a soap opera on TV might bring on a heart attack.

What is the truth? A difficult one, because until recently anecdote trumped any other real evidence we had. Now though, a systematic review and two randomised trials light up the darkness with a few rays of evidence. What we need to know is whether people can stick to the diet, whether they lose weight, and whether there are any untoward effects arising from the diet.

Systematic review [1]

A search strategy was used to locate any studies in English that examined the use of low carbohydrate or ketogenic diets. Any study architecture was eligible, and eventually reports of 94 interventions were located. As many as half were very small, with fewer than 30 participants, and some studies had as few as two participants. The largest study had 162 participants, and few had as many as 100.

Some trials were randomised. In most studies the duration of the diet was relatively limited, with few lasting as long as 100 days. Few studies examined daily carbohydrate consumption as low as 60 grams/day or less, and only five studies evaluated such low carbohydrate consumption for more than 90 days.

Given all this, any analysis could be little more than speculative. What emerged, though, was that among obese people, weight loss was associated with longer diet duration and restriction of calorie intake rather than carbohydrate content. There was no significant effect on serum lipids, fasting glucose or insulin levels, or blood pressure.

RCT in 132 people with severe obesity [2]

Here 132 people with a mean BMI of 43 kg/sq metre were randomised to six months of either a low carbohydrate diet

of 30 g/day or less, or a low fat US guideline diet with a 500 calorie daily deficit and fat content of 30% or less of total calories. The diet groups attended weekly teaching groups for a month, and monthly sessions for five months. No specific exercise programme was recommended.

Results

The average age of subjects was 53 years, and their average weight was 131 kg. About 40% had diabetes, 60% were on antihypertensive treatment, and 40% were treated for hyperlipidaemia. Subjects on the low carbohydrate diet reduced their calorie consumption by an average of 460 calories a day to 1,600 calories per day; in the low fat diet the reduction was less, by 270 calories per day, but again to 1,600 calories per day.

More people stayed on the low carbohydrate diet than on the low fat diet (Table 1), though the difference was not significant. The average weight loss was greater in the low carbohydrate (6 kg weight loss) than in the low fat diet (2 kg weight loss, Table 1). A weight loss of 10% or more occurred in 9 of 64 subjects on the low carbohydrate diet, compared with 2 of 68 subjects on the low fat diet. This implies a number needed to treat with low carbohydrate diet for six months of 9 (5 to 58) for a 10% weight reduction, compared with a low fat diet.

The major difference in serum lipids was a 20% reduction in serum triglyceride in those on the low carbohydrate diet. With the low fat diet there was an average reduction of 4%. There were no changes in total or lipoprotein cholesterol in either group.

Diabetic subjects on the low carbohydrate diet reduced fasting glucose by 9% in the low carbohydrate diet compared an average reduction of 2% on the low fat diet. Seven subjects in the low carbohydrate group had dose reductions in oral hypoglycaemic drugs or insulin by six months, while on the low fat diet one subject had had an insulin dose reduction, and one started oral therapy. This implies a number needed to treat with low carbohydrate diet for six months of 4 (2 to 10) for a reduction in diabetic therapy, compared with a low fat diet.

There were no changes in blood pressure with either diet. Two patients, both on the low carbohydrate diet, had hospital admissions. One was for chest pain unrelated to cardiac ischaemia, and the other was hyperosmolar coma due to poor compliance with diabetes therapy.

Table 1: Low carbohydrate and low fat diets compared - subjects remaining on the diet and mean weight loss over six months

Month	Percent remaining		Mean weight reduction (kg)	
	Low carbohydrate	Low fat	Low carbohydrate	Low fat
2	75	62	4.0	1.0
4	73	56	5.5	2.5
6	67	53	5.7	1.8

Table 2: Low carbohydrate and conventional diets compared - subjects remaining on the diet and mean weight loss over 12 months

Month	Percent remaining		Mean weight reduction (kg)	
	Low carbohydrate	Conventional diet	Low carbohydrate	Conventional diet
3	85	70	8.0	3.7
6	73	60	9.6	5.2
12	61	57	7.2	4.4

RCT in 63 people with obesity [3]

Here 63 people with a mean BMI of 34 kg/sq metre were randomised to 12 months of either a low carbohydrate diet (Atkin's diet), or a conventional diet with calorie restriction deficit and high carbohydrates, with fat content of 25% or less of total calories. Subjects had no counselling or other professional help, and none had diabetes.

Results

The average age of subjects was 44 years, and their average weight was 98 kg. More people stayed on the low carbohydrate diet than on the conventional diet (Table 2), though the difference was not significant. The average weight loss was greater in the low carbohydrate than in the conventional diet at three and six, but not 12 months (Table 2).

The low carbohydrate, but not the conventional diet, led to a 20% reduction in serum triglyceride, and about a 20% increase in HDL cholesterol, but not total or LDL cholesterol. There was no change in blood pressure in either group.

Comment

What are we to learn from all this? First, perhaps, that there is not a huge amount of evidence. What there is suggests that low carbohydrate diets are likely to deliver a larger

weight reduction, certainly at about six months. Moreover, more people on low carbohydrate diets stay on them for longer. Neither of the randomised trials did anything in particular about exercise, a very important component of lifestyle changes needed for sustained weight loss.

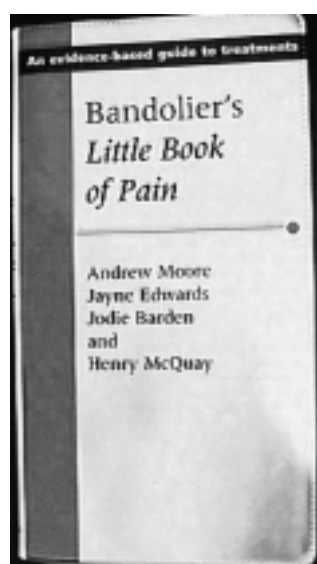
The higher proportions of protein and fat do not seem to adversely influence risk factors like total and LDL cholesterol, and probably improve risk factors by reducing triglyceride levels and perhaps increasing HDL cholesterol levels. There may be small changes to insulin resistance.

In the end it may come down to suitably matching a dietary regimen to an individual's taste. For some of us, a high protein diet, with bacon and eggs, steak, fish and cheese would be heaven. For others, purgatory. Perhaps now people who want or need to lose weight have more of a choice about what might best suit them.

References:

- 1 DM Bravata et al. Efficacy and safety of low-carbohydrate diets. A systematic review. JAMA 2003 289: 1837-1850.
- 2 FF Samaha et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. New England Journal of Medicine 2003 348: 2074-2081.
- 3 GD Foster et al. A randomized trial of a low-carbohydrate diet for obesity. New England Journal of Medicine 2003 348: 2082-2090.

BANDOLIER'S "LITTLE BOOK OF PAIN"



Bandolier's "Little Book of Pain" is a unique portable guide to evidence based pain treatments. The book has been developed from collecting systematic reviews and meta-analyses for the *Bandolier* Internet site, and has material on acute and chronic pain, migraine and headache, arthritis, cancer and palliative care, complementary and alternative therapies, and management issues. It starts with an easy guide to understanding EBM, so that everything is in perspective.

The book provides the evidence supporting the efficacy of a treatment, with a clinical bottom line at the top for the five-second read for those requiring immediate information, and a 10-minute read for those who want to know more.

Written by world leaders in the field of evidence based pain treatments, the book will be indispensable for the multi-disciplinary professionals managing acute and chronic pain in primary and secondary care, including GPs, nurses and pharmacists.

The book has 450 pages and costs £19.99. It is available from Oxford University Press (<http://www.oup.co.uk/isbn/0-19-263247-7>) from June 19, and from bookshops and other Internet sources.

PNEUMOCOCCAL VACCINATION

UPDATE

Bandolier 72 related a systematic review [1] concluding that pneumococcal vaccines were ineffective for most outcomes in most people, especially those more likely to have them in western countries. Other reviews confined to randomised trials [2] have largely confirmed this.

A problem, though, is that some outcomes, like bacteraemia or death from pneumococcal pneumonia, are rare (usually affecting less than 1%), so even though large studies have been done, there are few actual events. Of course, if the events are that rare or the difference between vaccine and placebo that small, the chance of a difference in clinically relevant outcomes will also be small. But the trials may have missed something important, so a revisit to a large epidemiological study [3] makes sense.

Study

This was a retrospective cohort study. The population was a health organisation in Washington State, in people at least 65 years old. They were followed from March 1998 to 2001 (three years). Records were examined for evidence of vaccination with pneumococcal polysaccharide vaccine, and for other information about health status, other diseases, and smoking status.

The primary outcome was hospital admission for community-acquired pneumonia, pneumonia where patients were not admitted (outpatient pneumonia), and pneumococcal bacteraemia. Analysis included assessment of various possible co-variables, like time since vaccination, smoking status, nursing home residence, or other conditions.

Results

There were 47,000 people with 127,000 years of evaluation, with two-thirds of this following pneumococcal vaccination. Hospital admission for confirmed community-acquired pneumonia occurred in 1,428 people, of whom 61 had pneumococcal bacteraemia. There were 3,061 cases of pneumonia not admitted, and 5,690 deaths from all causes.

There was no significant association between vaccination and the risk of hospital admission for community-acquired pneumonia, outpatient pneumonia, or death from any cause when the results were adjusted for age, sex, nursing home residence, influenza vaccination, smoking status and comorbid conditions (Table 1). Time since vaccination made no difference to the results.

The presence of pneumococcal bacteraemia was lower in vaccinated persons based on adjusted and unadjusted rates (Table 1). The unadjusted difference was 30 persons for every 100,000 vaccinated.

In immunocompromised persons (9,158), defined by presence of cancer, use of immunosuppressive medication, and chronic liver or renal disease, pneumococcal vaccination made no significant difference for any outcome. Neither was there any difference for immunocompetent persons with chronic lung disease.

Also reported was results with influenza vaccination. Influenza vaccination was associated with a significant reduction in the risk of hospital admission with community-acquired pneumonia (0.78, 95% confidence interval 0.65 to 0.95) and risk of death (0.68; 0.62 to 0.76) during the influenza season.

Comment

These results are broadly consistent with results of several meta-analyses of randomised trials, none of which showed any effect of pneumococcal vaccination on pneumonia. Meta-analysis did not show any effect on pneumococcal bacteraemia in elderly or at risk subjects [2], but based on many fewer subjects than in this cohort study, and with non-significantly reduced risk. So for this outcome there is again broad agreement.

What would be the impact of vaccinating older people? About 20% of the UK population is aged 65 or older. In a typical population of 100,000, universal vaccination of those aged 65 or older would prevent about six cases of pneumococcal bacteraemia over a period of a few years.

The authors concluded that their study supports the use of pneumococcal vaccine to prevent bacteraemic disease in adults aged 65 or older. Their conclusion was based mainly on a health economic study [4], whose main conclusion was that vaccination saved \$8.27 (about £5) and gained 1.2 quality-adjusted days of life per person vaccinated. The most unfavourable assumption was that the vaccination cost per quality-adjusted life-year ranged from \$35,822 for ages 65 to 74 years to \$598,487 for ages 85 years and older.

What is good is the agreement between a large and detailed cohort study and meta-analyses of randomised trials. Not everyone will be convinced by the argument that vaccination is worthwhile, and it is a topic that needs looking at with a cold and fishy eye, especially when newer, and hopefully better, vaccines come along. In the meantime, only very large cohort studies are likely to provide sufficient events to give better information on the effectiveness of the pneumococcal vaccines we have now.

Table 1: Pneumococcal vaccination and outcomes

	Hospital admission for pneumonia	Outpatient pneumonia	Pneumococcal bacteraemia	Death from any cause
Unvaccinated rate per 1000 patient years (%)	10.4	23.2	0.68	50
Vaccinated rate per 1000 patient years (%)	11.8	25.7	0.38	42
Fully-adjusted risk	1.1 (0.98 to 1.3)	1.0 (0.94 to 1.1)	0.53 (0.31 to 0.93)	0.94 (0.87 to 1.01)

References:

- 1 BG Hutchison et al. Clinical effectiveness of pneumococcal vaccine: meta-analysis. *Canadian Family Physician* 1999 45: 2392-93.
- 2 RA Moore et al. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. *BMC Family Practice* 2000 1:1 (<http://biomedcentral.com/1471-2296/1/1>)
- 3 LA Jackson et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *New England Journal of Medicine* 2003; 348: 1747-1755.
- 4 JE Sisk et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* 1997 278: 1333-1339.

PREVALENCE OF SCHIZOPHRENIC DISORDERS

How many people have schizophrenia or schizophrenic disorders? A systematic review using rigorous methodology derives reasonably consistent estimates both for prevalence and for incidence [1], and explores differences between different estimates.

Systematic review

Two databases were searched for English language studies published between 1980 and 2000. Studies were selected for inclusion based on several features.

They had to be community surveys of the general population, or, for incidence studies, case-register methods that surveyed at least primary care general medical services. The age range for included studies was adults between the ages of 18 to 65 years, though for incidence studies the age of 15 and over was used. Studies also had to have a reasonable size, and only those with a denominator sample of 450 or more were included. The diagnostic criteria were the ICD-9 or DSM-III systems or later, and case definition had to be explicit.

Results

Prevalence

Sixteen prevalence reports were found, examining mental disorders, with samples ranging from 500 to 20,000, and most used structured interviews administered by lay interviewers, with algorithms applied to derive diagnoses.

Best estimates for one-year and lifetime prevalence of schizophrenic disorders and schizophrenia are shown in Table 1. For schizophrenia, for instance, the best estimate for a one-year prevalence was about 340 per 100,000 adults.

There was little difference in rates between the sexes. Prevalence was influenced by world region, with Asian studies having lower rates (lifetime prevalence of 400 per 100,000 or below) than those in other regions (300 to 1,600 per 100,000).

Incidence

Eight studies provided one-year incidence rates for schizophrenia. The sizes ranged from 73,000 to over five million.

Most estimates of incidence were between five and 23 per 100,000, with a best estimate of 11 per 100,000 (95% confidence interval 8 to 16).

There was a tendency for more recent studies, with assessments in the 1990s, to have higher incidence rates, but this was not a strong trend.

Comment

What this paper does, apart from tell us much about prevalence and incidence of schizophrenic disorders, is to educate us more about methods. It is an object lesson on how to think through obtaining quality information because it has thought about what constitutes quality before starting the review.

What might these figures mean to a UK population? In every 100,000 people about 80,000 are aged 16 or more. That means we might expect there to be about 250 adults with schizophrenia at any time, with another eight or so being diagnosed every year.

It is also interesting to question whether standard textbooks agree with these estimates. *Bandolier's* bible, the Oxford Textbook of Medicine, provided an annual schizophrenia incidence of 0.1 or 0.2 per 1,000, and a prevalence of 3 per 1,000. That's 10-20, and 300 per 100,000 respectively, which is in excellent agreement with the figures in this systematic review.

References:

- 1 EM Goldner et al. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. *Canadian Journal of Psychiatry* 2002 47: 833-843.

Table 1: Prevalence of schizophrenic disorders, schizophrenia and schizophreniform disorder in adults

Diagnosis	Prevalence per 100,000 adults (95% CI)	
	One year	Lifetime
Schizophrenic disorder	600 (380 to 910)	1450 (80 to 2370)
Schizophrenia	340 (220 to 500)	550 (370 to 800)
Schizophreniform disorder	90 (50 to 140)	110 (60 to 170)

INHALED CORTICOSTEROID DOSE

There is little more rewarding than to see good evidence used to make some assessment of the balance of benefit and harm in a treatment in terms we can understand. One such comes from Australia, where there was concern about the common use of high doses of inhaled corticosteroids in asthma. Using evidence from Cochrane reviews made this possible.

Review

This review of reviews sought systematic reviews from the Cochrane Database only, and found six that compared inhaled corticosteroids with either placebo or different doses of inhaled corticosteroids for chronic asthma. Efficacy outcomes were peak expiratory flow, FEV1, night waking and rescue beta-agonist use, together with withdrawal because of worsening asthma. Adverse events were also examined.

Results

The response of efficacy and harm with increasing dose of inhaled corticosteroids could only be assessed for fluticasone. For neither beclomethasone nor budesonide were there were insufficient studies covering a range of doses.

For fluticasone, efficacy increased with dose. There were small but clinically useful improvements in peak expiratory flow (by 30 to 45 L/minute more than placebo) and FEV1 (by 0.3 to 0.5 litres more than placebo) as the daily dose increased from 100 µg/day to 1000 µg/day. There were also small improvements in night waking.

Numbers needed to treat could be calculated for withdrawal because of worsening asthma. These were 2.9 at 100 µg/day improving to 2.0 at 500 to 1000 µg/day (Table 1).

At low daily doses of 100 or 200 µg/day, neither dysphonia nor oral candidiasis were much of a problem, affecting perhaps an additional one person per hundred treated, and with NNTs of about 100.

At daily doses of 500 µg and above, numbers needed to harm (NNH) fell to levels of about 20 or below, indicating that for every 100 patients treated with these doses, about an additional 5 would experience dysphonia and 5 would experience oral candidiasis.

Table 1: NNT for efficacy and NNH for harm with increasing daily doses of inhaled corticosteroid

Fluticasone (µg/day)	NNT	NNH	
	Withdrawal because of worsening asthma	Hoarseness or dysphonia	Oral candidiasis
100	2.9 (2.4 to 3.4)	150 (40 to 1140)	90 (27 to 750)
200	2.4 (2.2 to 2.8)	131 (50 to 420)	61 (22 to 260)
500	2.0 (1.7 to 2.3)	23 (15 to 52)	21 (14 to 46)
1000	2.1 (1.8 to 2.4)	17 (11 to 35)	23 (14 to 75)
2000	—	11 (6 to 100)	6 (4 to 17)

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Subscription rates are £36 in the UK and £72 overseas, but with significant discounts for bulk purchase, for instance for healthcare organisations.

Comment

The paper concludes that use of lower doses of inhaled corticosteroids would be associated with lower adverse events without much loss of efficacy. What *Bandolier* found interesting when doing a search was that there was little obvious literature about oral candidiasis and inhaled corticosteroids. Yet adverse events like this can have important impact on cost of treatment and patient acceptability.

The real pleasure comes from an intelligent use of evidence to improve outcomes and, because of fewer adverse events, reduce costs.

References:

- 1 H Powell, PG Gibson. Inhaled corticosteroid doses in asthma: an evidence-based approach. Medical Journal of Australia 2003 178: 223-225.